A Cost Effectiveness Analysis of Calcium and Vitamin D Supplementation, Etidronate, and Alendronate in the Prevention of Vertebral Fractures in Women Treated with Glucocorticoids

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ABSTRACT. ***Objective.*** To assess the relative costs and benefits of calcium and vitamin D supplements, cyclic etidronate, or alendronate in the prevention of vertebral fractures for women and with normal bone density and osteopenia who are about to initiate moderate dose glucocorticoid treatment.

Methods. Using a decision analysis model, we evaluated the following patients: 4 hypothetical cohorts: 30-yr-old women with normal lumbar spine (LS) bone mineral density (BMD) (t score = 0), 50-yr-old women with borderline osteopenia (t score = –1), 60-yr-old women with moderate osteopenia (t score = –1.5), and 70-yr-old women with severe osteopenia (t score = –2) treated with a mean prednisone dose of 10 mg/day for one year. The main outcomes included the development of vertebral fractures 10 years after glucocorticoid treatment and at age 80 (life-time risk) and direct and indirect costs.

Results. At 10 years, calcium and vitamin D supplements decreased fracture rates by 30–50% at a minimal cost (US$800 or less per vertebral fracture avoided) or at a cost saving compared to no treatment for women with osteopenia (t score –1 to –2). Etidronate and alendronate are most cost effective in women with borderline osteoporosis (t scores of –1.5 and –2) in the 10 year analysis. In the life-time analysis, calcium and vitamin D treatment yielded a cost savings compared to no treatment for all groups with osteopenia. Etidronate decreased fracture rates further in all groups at a cost of less than $2,000 per fracture prevented. Alendronate reduced the fracture risk further at cost of $3,000–7,000 per fracture avoided.

Conclusion. Calcium and vitamin D supplements and low cost bisphosphonate regimens such as cyclic etidronate decrease the life-time vertebral fracture risk at acceptable costs and should be considered when initiating glucocorticoid treatment for women who do not have osteoporosis. (J Rheumatol 2003;30:132–8)

Key Indexing Terms:

CORTICOSTEROIDS	GLUCOCORTICOIDS	OSTEOPOROSIS
BISPHOSPHONATES	CALCIUM	VITAMIN D

Due to their potent antiinflammatory effects, glucocorticoid medications are commonly prescribed on a longterm basis to treat a variety of allergic and inflammatory diseases as well as to prevent rejection after organ and bone marrow transplantation. Longterm glucocorticoid use is associated with significant toxicities; one of the most important of these is an increased risk of osteoporosis and fractures[1-8]. Glucocorticoids have the greatest detrimental effects on trabecular bone increasing vertebral fracture rates at least 4-fold and femoral fracture rates by 50–200%[5-8]. Women are at higher risk for fractures because of lower bone mass, and postmenopausal women who have not received hormone replacement therapy (HRT) are at the highest risk[9,10].

Several agents are available to prevent bone loss associated with glucocorticoid use including calcium, vitamin D, estrogen, bisphosphonates, and calcitonin. Calcium and vitamin D supplements may prevent bone loss in patients receiving longterm low dose glucocorticoid treatment[11]. However, they do not completely prevent bone loss at all sites in all patients when glucocorticoid treatment is initiated at higher doses[9,12,13]. Recent clinical trials have shown that bisphosphonates (etidronate, alendronate, and risedronate) are more effective than calcium and vitamin D supplements in preventing or attenuating glucocorticoid induced bone loss[9,10,14,15]. There are no prospective data about the effects of HRT on fracture rates or bone density when used at the initiation of glucocorticoid treatment[16,17] and there is controversy about the efficacy of calcitonin[18-21].

There is general agreement that patients with established osteoporosis should receive therapy to limit further bone loss when starting glucocorticoid treatment but debate about

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which preventive treatments should be used for women who do not have osteoporosis[22-25]. We developed a model to assess the relative costs and benefits of treatment with calcium and vitamin D supplements alone or with a bisphosphonate (etidronate or alendronate) in the prevention of vertebral fractures for hypothetical group of women without osteoporosis with varying ages and baseline bone densities who are initiating moderate dose glucocorticoid treatment.

MATERIALS AND METHODS

Definitions. The model estimates the costs and benefits of preventing glucocorticoid-induced osteoporosis and fractures in the vertebral spine for women. The World Health Organization's (WHO) definition of osteoporosis[26] is based on a comparison of current bone mineral density (BMD) to the mean bone density of a group of young adults of the same gender. BMD is defined as normal if it is greater than or equal to one standard deviation (SD) below the mean BMD of young adults of the same gender (t score ≥ –1). Osteopenia is defined as BMD between 1 and 2.5 SD below the young mean BMD (–1 > t score ≥ –2.5), and osteoporosis is BMD lower than 2.5 SD below the young mean (t score < –2.5).

Patients. The effect of glucocorticoid treatment on lumbar spine BMD (LS BMD) was simulated for 4 hypothetical cohorts of women: (1) 30-yr-old women with normal vertebral BMD (LS BMD t score = 0); (2) 50-yr-old women with borderline osteopenia (LS BMD t score = –1); (3) 60-yr-old women with moderate vertebral osteopenia (LS BMD t score = –1.5); and (4) 70-yr-old women with severe vertebral osteopenia (LS BMD t score = –2). The model only addressed outcomes for Caucasian women because most of the data about the relationship between fracture risk and bone density are drawn from studies including predominantly Caucasian women.

Glucocorticoid treatment. Initiating one year of prednisone treatment at a mean dose of 10 mg/day.

Strategies. Four strategies were used for one year: (1) no treatment; (2) calcium (500–1000 mg/day) and vitamin D (400 IU/day); (3) cyclic etidronate (400 mg/14 days of every 3 months); and (4) alendronate (10 mg/day). Because the costs and benefits of risedronate and alendronate are similar, the cost effectiveness of these treatments overlaps and only alendronate was included in the model. The model included the cost and effects of alendronate 10 mg/day but recent studies in postmenopausal (PMP) women have shown equivalent effects of daily and weekly treatment on BMD in this group[27] and the costs are very similar. Because the 5 mg and 10 mg tablets of alendronate have similar cost but the 5 mg dose is less effective in increasing BMD, only the 10 mg dose was included in the model.

Endpoints. The endpoint of the analysis was the development of a vertebral fracture and the associated direct and indirect costs to the patient or insurer. Direct costs included the cost of medication and medical care for vertebral fractures. Indirect costs included lost salary due to fracture and the lost salary of the caretaker/spouse after a fracture.

Time horizon. Because fractures can occur early or years after glucocorticoid use, 2 time endpoints were considered: a 10 year endpoint (10 years from time of treatment) and a life-time endpoint (from initial treatment with glucocorticoids to age 80).

Change in BMD. It was assumed that bone loss in the first year depended on the treatment strategy as outlined in Table 1. The effect of each treatment strategy on percent change in BMD was estimated from a review of published clinical trials of prevention of glucocorticoid-induced osteoporosis[9,10,12-14,18]. The inclusion criteria for studies were: (1) a randomized, controlled trial, (2) with subjects starting glucocorticoid treatment, (3) at a mean prednisone dose of at least 10 mg/day for one year. The change in LS BMD with each treatment strategy was estimated by summing the mean percent change in LS BMD from each clinical trial weighted by the number of subjects in that trial divided by the total number of subjects in trials using that agent. The estimate of the effect of calcium and vitamin D was based on studies in which the combined regimen was used in the treatment or placebo group.

Table 1. Percent change in lumbar spine BMD for each year of the analysis by treatment group.

	No Treatment (%)	Calcium/ Vitamin D (%)	Etidronate (%)	Alendronate 10 mg/day (%)
Year 1	–7	–2	1	3
Year 2	–1	–1	0	0
Age 50–55	–2	–2	–2	–2
All other years	–0.5	–0.5	–0.5	–0.5

Bisphosphonates are retained in bone for long periods of time and prevent further bone loss for up to a year after treatment[28,29]. We estimated that the change in LS BMD in the second year was 0% for the alendronate and etidronate treatment and –1% for the calcium and vitamin D and no treatment groups[11]. Loss of bone density in subsequent years was estimated to be at a rate of 0.5% per year except for ages 50–55 when the rate of bone loss increased to –2% per year because of accelerated bone loss due to menopause without HRT.

Probability of developing osteoporosis. Based on normal data from dual energy x-ray absorptiometry (DEXA) databases, a 10–12% change in LS BMD was considered equivalent to a change of 1 in the BMD t score. As shown in analysis of data from clinical trials, change in BMD from glucocorticoid treatment is usually normally distributed[9,10,14,15]. Using these assumptions, the distribution of BMD t scores at the end of year 1 for each group of women with a particular treatment was estimated from the baseline BMD t score and the mean and SD of change of BMD for that treatment (Table 1). The proportion of women with a t score of less than –2.5 at the end of the first year was calculated using standard normal distribution tables. For example, 30-year-old women with a BMD t score of 0 and no preventive treatment in the first year of glucocorticoid treatment would lose 7 ± 5% of LS BMD (Table 1) resulting in a change of t score of –0.7 ± 0.5. The proportion of women with t scores less than –2.5 was estimated using standard normal distribution tables (x = [–2.5-mean t score]/SD). For each year of followup, the distribution of BMD for each group was changed by the amount listed in Table 1. Using this method, the proportion of women in each group with osteoporosis was calculated for each year of followup.

Vertebral fracture rates. Only vertebral and not femoral fractures were used as an endpoint for this analysis. Glucocorticoid use has a stronger association with vertebral than femoral fractures and there is little prospective data about the incidence of femoral fractures in glucocorticoid users. Ross and colleagues reported a yearly vertebral fracture rate of 4–12% among non-glucocorticoid treated women age 65 and older with established osteoporosis[30]. Liberman reported that 8% women with osteoporosis (t score < –2.5) over the age of 65 and 4.7% of women 65 or younger receiving a calcium supplement had a new vertebral fracture after 2 years[31]. In prospective studies of glucocorticoid users, the yearly fracture rate varied from 3.5 to 20% in control groups receiving calcium with or without vitamin D[9,10,15]. Saag and colleagues reported a yearly vertebral fracture incidence of 7.6% in PMP women and 0 in premenopausal women who were taking glucocorticoids (a group of new and chronic users) and were receiving calcium and vitamin D supplements[9]. Naganthan reported that 36% of patients age 65 or over who had received glucocorticoid treatment for > 6 mo had a prevalent vertebral fracture[32]. The vertebral fracture rate is dependent on age as well as BMD and the relative risk of fracture doubles for every 10 year increase in age independent of BMD[33]. Using these data, we conservatively estimated a yearly vertebral fracture rate of 4% in the oldest group of women and decreased the fracture risk by half for every 10 year decrement in age (Table 2).

The number of vertebral fractures per year was calculated by multiplying the age specific yearly fracture rate by the proportion of women in each group who were osteoporotic (LS BMD t score < –2.5) that year. Because women

Table 2. Yearly vertebral fracture rate by age for women with lumbar spine BMD score ≤ –2.5.

Age, yrs	Rate (%)
30–39	0.25
40–49	0.5
50–59	1
60–69	2
70–79	4

could have more than one fracture event per vertebra, the cumulative incidence of fractures would be expected to be greater than the prevalence of fractures at the end of the time period. The fracture risk was not adjusted for a previous fracture in the same patient. It was assumed that only one third of vertebral fractures were symptomatic and incurred cost[34,35].

Using a spreadsheet, the number of fractures per year and their associated direct and indirect costs were calculated and cumulative data on fractures and costs at 10 years and at age 80 were generated for each hypothetical cohort of women. We adjusted the data yearly for expected mortality[36-38]. Using US census data[37], the proportion of women employed for pay was estimated for each age group.

Although vertebral fractures have been associated with significant declines in quality of life and may be associated with higher mortality, there is debate about how to estimate the magnitude of these effects[39-45]. In this analysis, we did not assume any quality of life or survival differences due to a vertebral fracture. An average of 38 days of disability has been reported in women in a clinical trial who had a symptomatic fracture and this was the period of disability used in this analysis[40]. In addition, we estimated that one week of caretaker's time was needed for each symptomatic fracture. A sensitivity analysis was also performed and excluded all these indirect costs. Because instruments are still in development to assess the effects of fracture on quality of life or quality adjusted life years (QALY)[46-48], we used cost per vertebral fracture avoided as the outcome as suggested by Dere[49] rather than cost per QALY saved.

Costs. The drug costs were based on 2000 average wholesale prices of calcium 1000 mg (from calcium carbonate) and 400 IU of vitamin D from a multivitamin, etidronate (400 mg tab for 14 days every 13 weeks), and alendronate (70 mg/wk) (Table 3). Since each strategy was assumed to have the same extent of laboratory monitoring, these costs were not included. The cost of a symptomatic vertebral fracture was estimated at US$840[35]. The cost of LS BMD (measured by DEXA) was not included because all patients were assumed to have a BMD study at the start of glucocorticoid treatment. Future costs were discounted at a rate of 3% per year. Assumptions are listed in Table 4.

RESULTS

The results of the analysis 10 years after glucocorticoid treatment and at age 80 (life-time analysis) are presented in Table 5. The column to the far right lists the cost of each strategy per additional vertebral fracture avoided compared to the previous treatment (marginal fractures) with the least expensive treatment listed first. When a treatment is listed before no treatment, then it yields a cost saving compared to no treatment. Dominated indicates a strategy that has no additional benefits "but incurs" additional cost when compared to the previous strategy. The analysis was based on cost per vertebral fracture avoided but the proportion of women with osteoporosis is listed for additional information. The results for the 70-year-old women (LS BMD = –2) are identical in the 10 year and life-time analysis because 10 years after treatment these women will be age 80.

Table 3. Costs

	Cost (US $)
Calcium and vitamin D*	35
Etidronate 400 mg for 14 days every 3 mo*	275
Alendronate 10 mg/day*	762
Progesterone 5 mg/day*	187
Conjugated estrogen 0.625 mg/day*	75
Vertebral fracture	840
Yearly salary (women)[33]	23,000
Yearly salary (men)[33]	36,000

* Average wholesale price for one year, Drug Topics Redbook, 2000.

Table 4. Additional assumptions used in the design of our model.

One third of vertebral fractures are symptomatic[35]
38 days of disability per clinical vertebral fracture[40]
1 week of caretaker time per symptomatic vertebral fracture[39,41,44]
Change in vertebral BMD secondary to GC treatment is normally distributed[9-15]
Proportion of women working at different ages[37]

Ten year endpoint. Because the model estimates that fractures do not occur in women with normal BMD (LS BMD t score = 0) receiving moderate dose glucocorticoid treatment at 10 years, no therapy is cost effective in this group (Table 4). Calcium and vitamin D treatment lowers fracture rates by 30–50% for the 3 groups of women with LS BMD t scores ranging from –1 to –2 (osteopenia) at a cost of approximately $100 or less per fracture avoided or at a cost saving (lower cost than no treatment). Etidronate treatment further reduces the fracture rate but is most cost effective ($838 per fracture avoided) in the oldest group of women (age 70) who also have the lowest BMD (t score of –2) and the highest fracture rate (4%). Alendronate further decreases the fracture risk but at higher cost (> $7,000 per fracture avoided) in all groups.

Life-time analysis. When the life-time vertebral fracture risk is used as the endpoint (Table 5), calcium and vitamin D supplementation decreases fracture risk by 12–30% in all groups at a cost saving or minimal cost (< $250 per fracture avoided) when compared to no treatment. The addition of cyclic etidronate further decreases fracture risks substantially (an additional 18–50%) at a cost of less than $2,000 per vertebral fracture avoided for all groups. Weekly alendronate treatment further lowers rate by an additional 25–50% but at greater costs ($4,000–$8,000 per fracture avoided).

Excluding indirect costs. A sensitivity analysis was performed including only the costs of medication and fractures and excluding the indirect costs of patient and caretaker salary (data not shown). The results of the analysis were very similar because of the low cost of the relatively brief fracture associated disability.

Table 5. Main results.

Strategy	Cost per Person ($)	Marginal Cost ($)	Osteoporosis (%)	Vertebral Fractures	Marginal Fractures	Marginal CE ($)
10 year analysis						
			30 years old with LS BMD t score = 0			
No treatment	0	—	0	0	—	—
Calcium/Vit D	35	35	0	0	0	Dominated
Etidronate	275	245	0	0	0	Dominated
Alendronate	762	487	0	0	0	Dominated
			50 years old LS BMD t score = –1			
No treatment	46	—	83	6.1	—	—
Calcium/Vit D	50	3	58	3.5	2.6	115
Etidronate	282	232	21	1.1	2.5	9,280
Alendronate	762	485	16	0.7	0.4	121,125
			60 years old with LS BMD t score = –1.5			
No treatment	50	—	66	6.1	—	—
Calcium/Vit D	57	7	34	4.4	5.6	125
Etidronate	290	233	12	1.2	3.2	7,281
Alendronate	771	481	4	0.7	0.5	96,200
			70 years old LS BMD t score = –2			
Calcium/Vit D	134	—	73	33	—	—
No treatment	142	8	92	23	–10	Dominated
Etidronate	310	168	42	11	12	838
Alendronate	783	473	21	5	6	7,883
Life-time analysis						
			30 years old with LS BMD t score = 0			
No treatment	106	—	100	65	—	—
Calcium/Vit D	124	18	99	57	8	225
Etidronate	435	311	88	41	16	1,944
Alendronate	806	371	79	32	9	4,122
			50 years old with LS BMD t score = –1			
Calcium/Vit D	205	—	99	57	—	—
No treatment	234	29	100	65	–12	Dominated
Etidronate	455	221	88	41	24	1,563
Alendronate	863	408	79	32	9	4,533
			60 years old with LS BMD t score = –1.5			
Calcium/Vit D	129	—	73	28	—	—
No treatment	151	22	92	40	–12	Dominated
Etidronate	316	165	42	12	28	1,169
Alendronate	779	463	27	5	7	6,614
			70 years old with LS BMD t score = –2			
Calcium/Vit D	134	—	73	33	—	—
No treatment	142	8	92	23	–10	Dominated
Etidronate	310	168	42	11	12	838
Alendronate	783	473	21	5	6	7,883

Marginal CE indicates cost per fracture avoided compared with previous strategy. Dominated indicates a strategy that has no additional benefit but has additional cost. Osteoporosis indicates the percentage of women with osteoporosis. Vertebral fractures indicates number of vertebral fractures per 100 women.

Comparison with HRT. Although there are no prospective data on the effects of HRT on BMD when used at the initiation of glucocorticoid treatment (prevention trials), HRT was added to the analysis as a treatment option for PMP women (data not shown). We assumed that the effect of HRT on LS BMD was equal to that of alendronate based on prospective data in non-glucocorticoid treated PMP women[50]. We did not include assumptions about decrease in risk of cardiovascular events because of a lack of adequate data from which to make these estimates in glucocorticoid treated women[51]. In this analysis, assuming 100% compliance, HRT is more cost effective than both etidronate and alendronate because of low cost and high efficacy. But if HRT compliance is 10% less than compliance with etidronate, then HRT becomes a less cost effective strategy. Using limited data on the effects of calcitonin on BMD in glucocorticoid users, calcitonin was also entered into the model but because of higher cost and lower efficacy than etidronate, was not included in the final model.

Increasing fracture rate. Recent data suggest that fracture rates may be higher in glucocorticoid users than in PMP women with similar changes in BMD[8,32]. If the rate of fracture is doubled in each age group, etidronate and alendronate treatment are more cost effective in the life-time analysis (< $1,000 and $2,000–$4,000, respectively, per fracture prevented) (data not shown).

DISCUSSION

Factors contributing to the risk of developing glucocorticoid-induced osteoporosis include baseline BMD, dose and duration of glucocorticoid treatment, and future bone loss due to aging, menopause, immobility, and other metabolic and medical conditions. The amount of bone loss in a particular patient varies widely due to differences in these risk factors and other unidentified factors such as genetic makeup. The most important predictor of the development of fracture in glucocorticoid treated patients is the bone mass prior to treatment, so the elderly and postmenopausal women are at highest risk of fracture in prospective studies[9,10].

In this analysis, we examined the cost effectiveness of one year of treatment with calcium and vitamin D supplements, cyclic etidronate, or alendronate in the prevention of vertebral fractures in 4 cohorts of nonosteoporotic women with varying baseline LS BMD who were initiating treatment with moderate doses of glucocorticoids. Life-time as well as 10 year fracture risks were analyzed because fractures may occur early but also continue for years after glucocorticoid treatment[8]. Calcium and vitamin D supplementation is a low cost intervention that significantly decreases vertebral fracture risk in most groups of women in both the 10 year and life-time analysis. Etidronate (a low cost bisphosphonate) is a cost effective intervention when the life-time vertebral fracture risk is considered. Alendronate decreases the fracture rate further but at higher costs.

HRT and calcitonin have been used to prevent osteoporosis in glucocorticoid treated patients but there is limited prospective data on the effects of HRT on BMD in new glucocorticoid users and controversy about the effectiveness of calcitonin. In reality, the role of HRT may be limited by patient compliance and concerns about possible cardiovascular side effects. The cost effectiveness of calcitonin is limited by higher cost and lower efficacy.

As with all cost effectiveness studies, a primary limitation of this analysis is the accuracy of the estimates and assumptions. The estimates of bone loss were drawn from clinical trials that included men, premenopausal women, and PMP women, but studies suggest that bone loss from glucocorticoid treatment is comparable in men and women[9,11]. There were significant differences between trials in age, underlying disease, and dose and schedule of glucocorticoid use in subjects. Some trials enrolled small numbers of patients.

Another limitation is the accuracy of estimation of fracture rates. The assumptions used in the model for fracture rates were conservative: femoral fractures (which are less common and for which there is little prospective data about rates in corticosteroid users) were not included, and we assumed that fractures did not occur in women with BMD t scores > –2.5. Recent studies suggest that antiresorptive agents may have a greater effect on fracture risk than is explained by changes in BMD[52-54]. As shown in the sensitivity analysis, all the treatments in the model may be more cost effective in preventing fractures than estimated in this analysis.

Finally, projections of life-time bone loss and fracture risk are also limitations to the generalizability of the results of this analysis. The analysis is based on only 2 years of BMD and treatment data. Individual women who receive glucocorticoid treatment will have different rates of bone loss and fracture rates than projected in the model because of concurrent risk factors such as additional glucocorticoid treatment, immobility, use of hormone replacement therapy, and nutritional and genetic factors that will accelerate or ameliorate life-time bone loss. The purpose of developing this model is not to specify treatment for individual patients with varying diseases and patterns of glucocorticoid use but rather to assess average costs and benefits using conservative estimates of life-time bone loss. Treatment of patients should be individualized based on their personal risk factors, economic factors, and preferences. Glucocorticoid-induced bone loss is the most common cause of secondary osteoporosis. Women are more likely to receive glucocorticoid treatment and are at greater risk of fractures. Bone loss is greatest during the first 6 months of treatment so early preventive measures should be implemented for patients at risk. Despite this, studies show that the majority of glucocorticoid treated patients receive no preventive treatment, PMP women who are not yet osteoporotic are least likely to be treated, and there is significant variation in use of preventive agents by physician specialty[55–59].

Although studies suggest that it is not cost effective to use newer bisphosphonates to prevent bone loss in PMP women until they have osteoporosis (unless there are other risk factors), preventive therapy for glucocorticoid-induced bone loss is more cost effective for a number of reasons. First, the treatment to prevent bone loss can be limited to the period of glucocorticoid exposure, which will be only 1–2 years in some patients, and therefore limits cost. In addition, fracture risks in glucocorticoid treated patients is high and can occur early in glucocorticoid treatment[8]. Thus, a limited treatment intervention in this high risk group can decrease life-time fracture rates at acceptable costs.

This analysis demonstrates that calcium and vitamin D supplementation is a cost effective strategy to decrease vertebral fracture risk and that etidronate and alendronate further decrease the life-time fracture risk. These treatment strategies should be considered for women who do not have osteoporosis at the time glucocorticoid treatment is initiated to prevent bone loss and irreversible changes in bone architecture.

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